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14. ABSTRACT

The goal of this work is to use electrical microstimulation to provide artificial proprioception for individuals using Brain-Machine Interfaces (BMIs), and particular for spinal cord injury. Preliminary results suggest that performance levels with combined artificial feedback and visual feedback exceeds that achievable with visual feedback alone. We have also developed new and powerful schemes to remove the electrical artifacts due to microstimulation from the neural recordings used for BMI control. This allows us to move to a much more efficient paradigm with continuous brain “read out” for BMI control of an external device and “write in” for artificial sensory feedback from that device.

15. SUBJECT TERMS

Spinal cord injury; brain-machine interfaces; artificial feedback; proprioception; somatosensation; microstimulation; movement control

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1. INTRODUCTION:

Spinal cord injury (SCI) often leads to both the loss of ability to move ones limbs and the loss of sensation from the limbs. One key component of this lost sensation is proprioception, the feeling of where the body is in space. The importance of proprioception is often not appreciated; without it, we are unable to move normally. Even if there were therapies that could restore movement to spinal cord injured patients, without proprioception those movements will be slow, clumsy and uncoordinated. The goal of this work is to restore proprioception for these individuals. In particular, we are focusing on restoring proprioception in the context of brain machine interfaces (BMIs), in which neural activity from the brain's motor centers is monitored and used to guide control of an assistive device such as an orthotic limb. We are working to develop and test a "bi-directional" BMI, which both monitors neural activity in motor areas of the cerebral cortex and delivers artificial proprioceptive feedback via intracortical microstimulation (ICMS) to a somatosensory cortical area. Since these precise neural patterns needed to evoke the correct proprioceptive sense is not known in advance, we are focusing on the brain's ability to learn to interpret new signals. In previous work, we showed that the brain can learn to interpret arbitrary patterns of ICMS activation and can use those patterns to guide movement (Dadarlat, O'Doherty, and Sabes, *Nature Neuroscience*, 2015). We are working to extend this approach to a bi-directional BMI.

2. KEYWORDS:

Spinal cord injury; brain-machine interfaces; artificial feedback; proprioception; somatosensation; microstimulation; movement control

3. ACCOMPLISHMENTS:

What were the major goals of the project?

<u>Specific Aim 1: Determine whether animals can learn to use artificial proprioception</u>

Artificial proprioception is delivered The ICMS feedback signal will not at first be meaningful to the animals. However, that signal will correlate on a millisecond timescale with visual feedback of the virtual limb. Based on the previous work (Dadarlat et al., 2015), we expect these correlations to drive naturalistic integration of ICMS. After learning, we will use behavioral measures to determine how well the animal can interpret the ICMS signal, alone and combination with visual feedback. We will determine whether ICMS and vision are integrated in a minimum-variance manner, as expected for "natural" sensory signals.

- Major Task 1.1: Train animals in basic procedures (Months 1-6)
  - This task is complete.
- Major Task 1.2: Experiment 1 – data collection (Months 1-13)
  - <u>Monkey 1</u>: In our first experiment with Monkey 1, we found that the animal's performance with artificial proprioception (delivered via ICMS) and vision was improving, compared to that achieved with vision alone. The pace of learning was comparable to our earlier published study. However, as reported in the quarterly report, we encountered a technical setback: the electrode array in M1 of Monkey 1 failed, no longer providing robust enough single unit recordings to provide high-quality BMI control. We have therefore explanted the array in this animal. We will implant new arrays in the next quarter.
  - <u>Monkey 2</u>: From our experience with Monkey 1, we are confident that Monkey 2 can be transitioned to brain control quickly after the implantation of electrode arrays. As

previously reported, we decided to delay implantation of Monkey 2 in order to take into account the results of the main experiment with Monkey 1. Because the electrode arrays have finite longevity (see above), this will maximize the use of that time for Monkey 2. We plan to implant Monkey 2 in the next quarter as well.

- Major Task 1.3: Experiment 1 – data analysis (Months 4-22)
    - We have made considerable progress on data analysis, and expect to be nearly on target with this task, despite the delays in Major Task 1.2.
    - We have made use of the time afforded by the experimental delays to address a major challenge raised by the use of electrical stimulation. Stimulation creates a large electrical artifact that interferes with simultaneous recordings from motor cortex. We originally dealt with this issue by temporally separating the stimulation and recording intervals. We have now developed powerful new tools for removing the artifact from the recording signals (see below).

Specific Aim 2: Determine whether artificial proprioception improves BMI learning rate and asymptotic performance

Whether or not naturalistic integration is achieved in Aim 1, we expect that the addition of feedback signals directly to S1 will improve BMI performance. We will measure the learning rate for a new BMI controller, the asymptotic performance of that controller, and the long-term stability of control, and compare these measures for cases with and without artificial proprioceptive feedback.

- Major Task 2.1: Experiment 2 – data collection (Months 10-30)
    - The start of these experiments has been delayed due to delays in Major Task 1.2. We still expect to be able to accomplish the key elements of this experiment by the end of the funding period.
- Major Task 2.2: Experiment 2 – data analysis (Months 12-36)
    - This task will begin shortly after the start of Experiment 2.

What was accomplished under these goals?

Major Tasks 1.2-1.3: Experiment 1

Monkey 1 performed approximately 400 “training” trials a session (i.e., per day). These training trials consisted of BMI reaches with combined visual feedback and artificial proprioceptive feedback. The artificial feedback conveys the two-dimensional location of the BMI-controlled cursor via intracortical microstimulation stimulation (ICMS). The ICMS signal consists of multiple bi-polar pairs of electrodes (one acting as cathode, one as anode) delivering sequences of charge-balanced, biphasic current pulses. The frequency of the stimulation pulses is varied as a function of cursor position in the 2-D space, with 5 independent “channels” of directional information (i.e., using a redundant five basis vectors to encode two-dimensional space). The goal of these training trials was to allow the animal to learn to interpret the ICMS signal and integrate it into the relevant sensorimotor circuits.

We monitored progress toward that goal with a smaller number of “testing” trials, with a variety of feedback conditions. The most important comparison during this early stage of learning is between testing with visual feedback alone and testing with both visual feedback and artificial feedback (“STIM”). Results for the first experiment are shown Figure 1, for two performance metrics: average absolute Cartesian endpoint error and average absolute angular error in initial movement angle (with respect to a straight line).

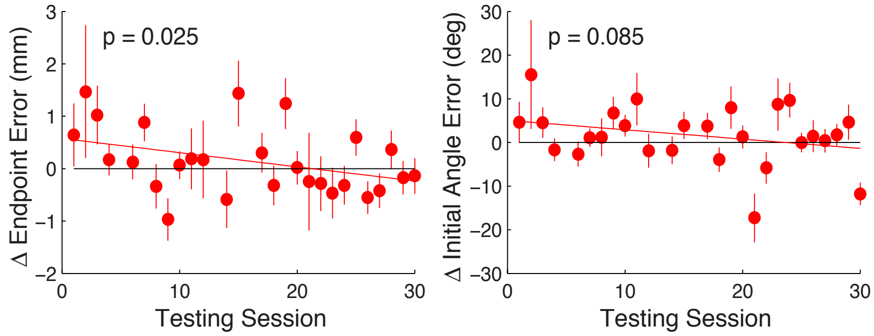


Figure 1. Differences between bimodal (VIS+STIM) and vision-only (VIS) trials, as a function of testing session, for two performance metrics. Smaller values equal better performance, so differences less than zero translate to better performance with the stimulation feedback on. p-values are for regression slopes.

Early in training, performance on both metrics was impaired by stimulation ($p<0.001$, 2-way ANOVA on session and feedback condition), but relative performance on the VS condition improved over time. By the last 10 sessions, VIS+STIM trials had significantly lower endpoint error ($p<0.03$; not corrected for multiple comparisons). It is notable that it took about 8,000 training trials (20 sessions) until performance improved with stimulation. However this results is on par with our earlier published study: improvement with feedback was not observed until about 13,000-15,000 trials, depending on the error metric (see Dadarlat, O'Doherty and Sabes, *Nature Neuroscience*, 2015). From that study, we expect that with more training (~30-40 additional sessions) the animal would have been able to make BMI reaches without vision, using only stimulation feedback.

This experiment was aborted due to electrode failure, and we recently explanted the original arrays. During the explantation surgery, we noted that that the S1 array was only superficially in the brain, having been pushed out by granulation tissue (as is commonly seen: Barrese, et al., *J Neural Eng.* 2013, 10(6):066014), which explains why we needed to stimulate multiple electrodes with high currents (100 uA) to elicit performance above chance at our preliminary detection task. We will restart training in both animals once new arrays are implanted in the coming quarter, and we expect that better array placement will result in better overall performance with the artificial ICMS feedback. Furthermore, we will take advantage of the restart to improve the experimental approach, in particular with the use of ICMS-artifact rejection, allowing for continuous control and feedback (instead of the interleaved control and feedback used in the first experiment).

<u>Major Tasks 1.2-1.3: ICMS Artifact Rejection</u>

A focus of our analysis has been on techniques to reject stimulation artifact, so that we can perform continuous stimulation and recording for BMI control. We have developed two approaches to solve this problem. First, as shown in Figure 2, we now can perform online artifact template subtraction from multiple channels.

In a second approach, we use an adaptive filter that takes advantage of our multielectrode recordings. In particular, for each electrode, we predict the stimulation artifact on that electrode by adaptively filtering the signals recorded on all of the remaining electrodes. This provides a remarkable robust artifact rejection scheme that generalizes across many different stimulation sites (Figure 3A) and performs even with highly non-stationary artifacts (Figure 3B). Furthermore, only about 10-20 recording sites are needed to achieve nearly asymptotic performance (Figure 3C).

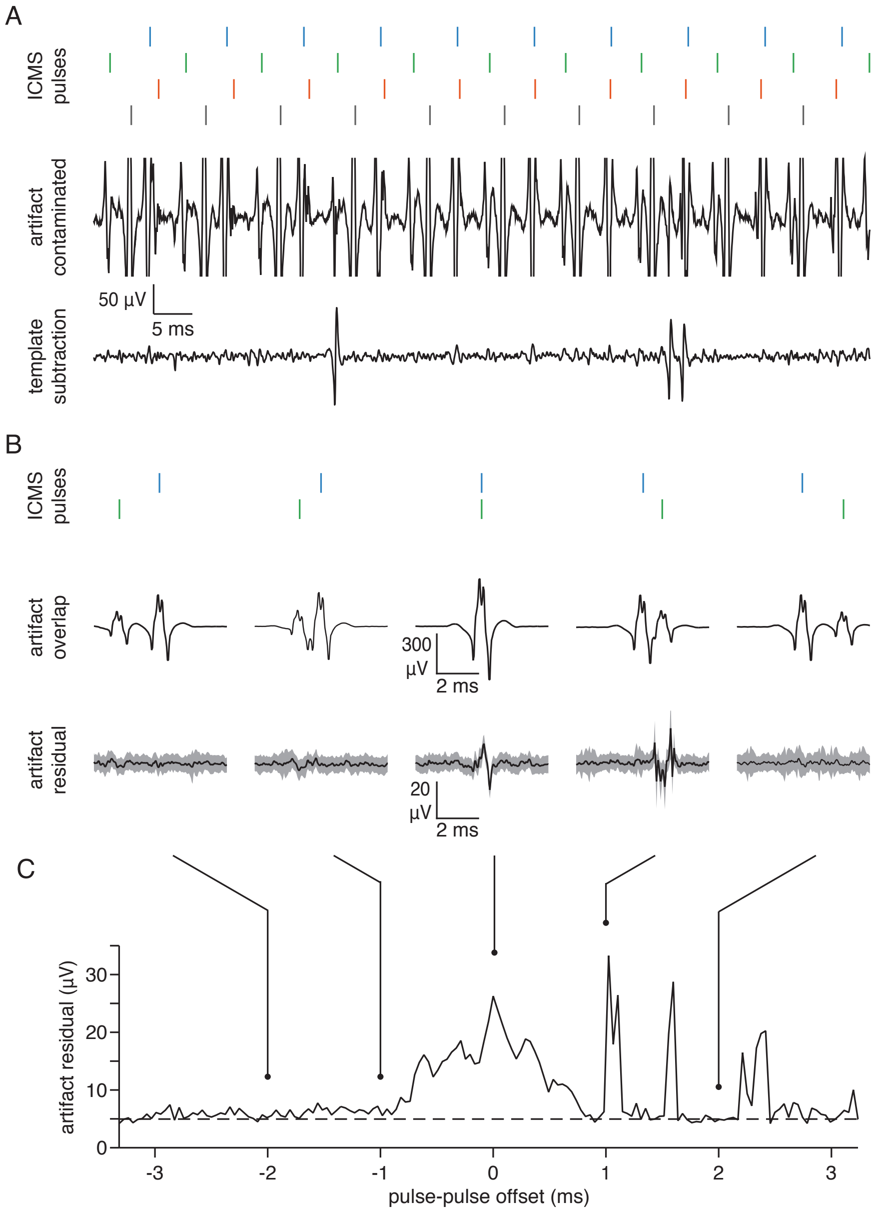


Figure 2. Stimulation artifact removed from multiple independent and simultaneous current sources, even when pulses completely overlap. (A) Pulse trains (top) were delivered to four electrodes in primary somatosensory cortex of a rhesus macaque, each with its own independent pulse repetition rate. The stimulation artifact contaminated concurrent recordings (middle) made in primary motor cortex. The artifact was modeled as linear and additive and was successfully removed (bottom) allowing action potentials to be detected. (B) The efficacy of the additive model is demonstrated by generating pulse trains (top) on multiple channels of stimulation at different temporal offsets with respect to each other. The resulting artifacts (middle) can be completely eliminated in many cases or greatly reduced in amplitude (bottom; note scale). Shaded region indicates standard deviation. (C) The residual signal after artifact removal is at the noise floor (dashed line) for many pulse offsets. For completely overlapping pulses the residual signal, while larger than the noise floor, is smaller than the amplitude of a typical extracellular action potential.

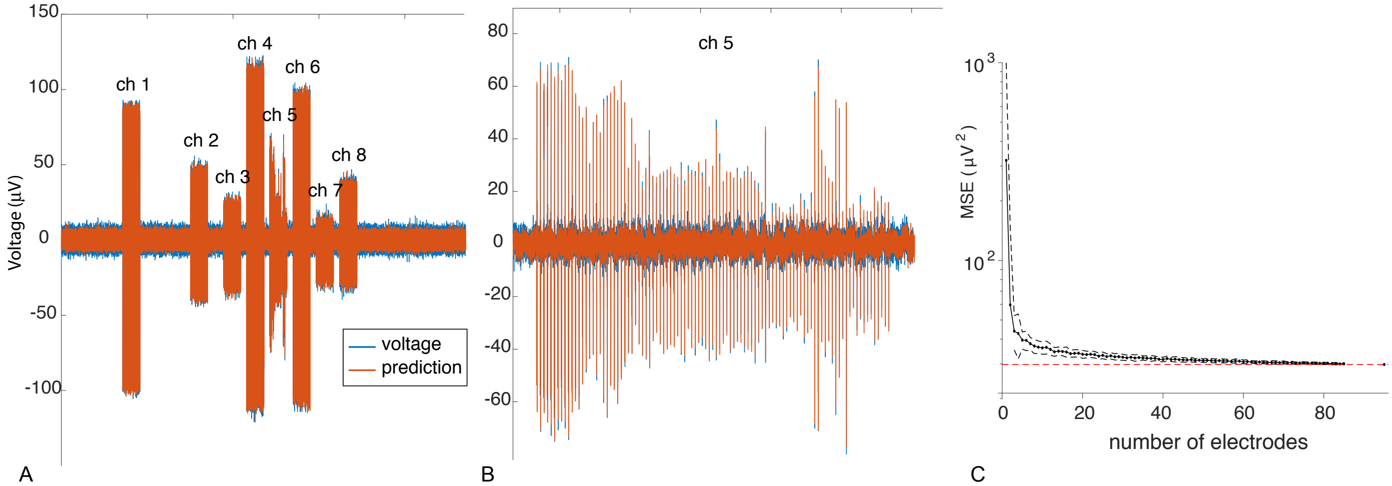


Figure 3. Stimulation artifact using adaptive multi-channel filtering. (A) Performance of the adaptive filter to remove a sequence of pulse trains delivered on different channels (1-8), showing that the same filter parameters work no matter which channels of stimulation are used. (B) The example of stimulation channel 5, at an enlarged scale, shows good artifact removal despite highly non-stationary artifact (presumably from a faulty stimulator channel). (C) Performance of the adaptive filtering method as a function of the number of electrodes used, showing that performance nears asymptotic levels with only a small number of recording electrodes (~10-20).

What opportunities for training and professional development has the project provided?

Nothing to Report.

How were the results disseminated to communities of interest?

Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?

Our effort in the next year will be focused on:

- Major Task 1.2 and 1.3
  - Implanting Monkeys 1 & 2
  - Completing Experiment 1 with both monkeys, using the improvements described above
  - Publishing our artifact rejection scheme
- Major Task 2.1 and 2.2
  - Starting Experiment 2, after completion of data collection for Experiment 1

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

- We have developed powerful new tools for removing artifacts from electrical recordings from the brain due to simultaneous brain microstimulation. We anticipate that these tools will be widely used in the field and will have a substantial impact on the improvement of bi-directional BMIs, i.e. devices that combine neural stimulation and recording.

- Our preliminary results suggest that the use of artificial sensory feedback delivered via brain microstimulation will improve performance of a BMI, compared to performance with visual feedback alone. If these results are replicated and expanded in upcoming experiments, we believe the impact for the BMI community will be great. In particular, this work would show that it is possible to obtain performance benefits even when it is not possible to be able to replicate the patterns of activity that would have occurred before spinal cord injury.

What was the impact on other disciplines?

- The artifact removal scheme will have impact beyond BMI applications. For example, the scheme will be useful for "causal" neuroscience experiments, in which stimulation is used to study the dynamics of brain circuits.

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

As reported in previous quarterly reports, we have experienced delays due the failure of the electrode implants in Monkey 1. We have already explanted those arrays and plan to implant new arrays in the coming quarter. While this has delayed progress on Specific Aim 1, it has also given us time to improve the experimental approach, as described in detail above. We anticipate that we will finish Aim 1 in the coming year.

Changes that had a significant impact on expenditures

Our spend rate was higher than originally planned in Year 1. The difference was due to the extra initial effort contributed by Drs. Sabes and Hanson in order to get the project started. We do not expect that this accelerated burn rate will persist into second year.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report (not applicable)

Significant changes in use or care of vertebrate animals.

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS:

Publications, conference papers, and presentations

Nothing to report

Website(s) or other Internet site(s)

Nothing to report

Technologies or techniques

As described above, we have developed powerful new tools for removing artifacts from electrical recordings from the brain due to simultaneous brain microstimulation. We expect that these tools will find wide application. We are currently preparing a manuscript describing these tools, which will be submitted soon. The manuscript will provide sufficient information for other groups to readily employ these techniques.

Inventions, patent applications, and/or licenses

Nothing to report

Other Products

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Name:	Philip Sabes, PhD
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	orcid.org/0000-0001-8397-6225
Nearest person month worked:	3
Contribution to Project:	Dr. Sabes is the PI. He has provided supervision and leadership for all aspects of the project
Funding Support:	1. DARPA/Case Western, iSens: Implanted somatosenso electrical neurostimulation

	2. DARPA, Unlearning neural systems dysfunction in neuropsychiatric disorders 3. DARPA, A new, scalable approach to high-bandwidth, minimally invasive neural recording and stimulation
Name:	Joseph O'Doherty
Project Role:	Postdoc
Researcher Identifier (e.g. ORCID ID):	orcid.org/0000-0001-8175-5699
Nearest person month worked:	1 (Dr. O'Doherty is also supported by a PVA fellowship wi largely overlapping aims. Therefore, Dr. O'Doherty is collectively contributing 100% effort to the Aims of this project.)
Contribution to Project:	Dr. O'Doherty has been principally responsible for performing the experiments and analyses in this project.
Funding Support:	1. Postdoctoral fellowship, Paralyzed Veterans of America
Name:	Timothy Hanson
Project Role:	Development Engineer
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	Mr. Hanson has provided technical support for all aspects of this project
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Sabes Active:
W911NF-15-2-0054 5/15/2015-6/14/2017
DARPA
A new, scalable approach to high-bandwidth, minimally invasive neural recording and stimulation

N66001-15-C-4014 1/16/2015-4/28/2016
Case Western Reserve University (DARPA)
iSens: Implanted somatosensory electrical neurostimulation and sensing

The latter of these is new in the last year.

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

See attached Quad Chart.

9. APPENDICES:

Nothing to report

Restoring Proprioception via a Cortical Prosthesis: A Novel Learning-Based Approach

SC130074
W81XWH-14-1-0510

PI: Philip N. Sabes **Org:** UCSF **Award Amount:** $710,683

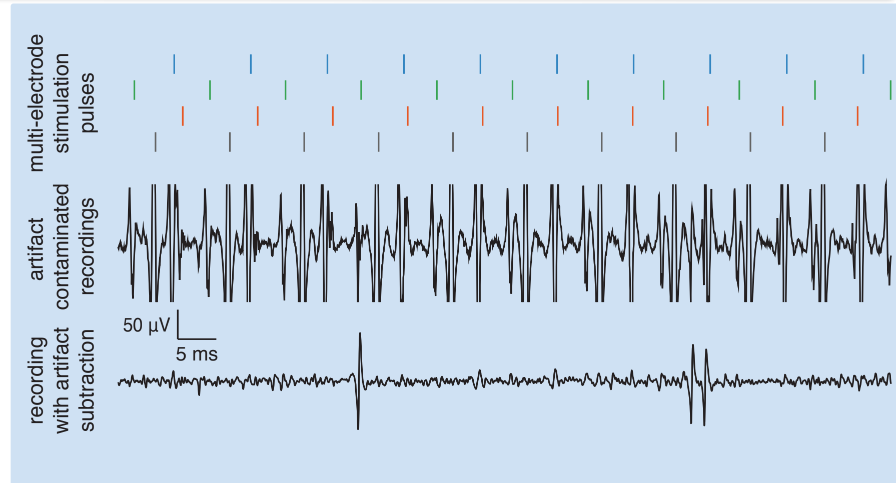
Study/Product Aim(s)

• Determine whether animals can learn to use artificial proprioception delivered via intracortical microstimulation (ICMS) to primary somatosensory cortex

• Determine whether artificial proprioception improves brain-machine interface (BMI) learning rate and asymptotic performance

Approach

A key factor that has limited performance of neuroprostheses is the lack of natural proprioceptive feedback. Our objective is to develop a learning-based approach for providing artificial proprioception, taking advantage of the brain's capacity for plastic reorganization.



Our refined our artifact rejection scheme removes stimulation-induced recording artifacts due to multi-electrode stimulation. This will permit a much more efficient closed-loop control scheme with continuous and simultaneous feedback and control.

Timeline and Cost

Activities CY	14	15	16	17
1.1: Train animals in basic procedures				
1.2: Expt. 1 – artificial feedback with learned BMI control: data collection				
1.3: Expt. 1 –data analysis				
1.2: Expt. 2 – artificial feedback while learning BMI control: data collection				
1.3: Expt. 2 –data analysis				
Estimated Budget ($K)	**$55**	**$189**	**$257**	**$211**

Updated: 29 October 2015

Goals/Milestones

CY14 Goal – Behavioral Training

☑ Preliminary, basic behavioral training

CY15 Goals – Demonstrate artificial feedback with learned BMI

☐ Perform Experiment 1 with Monkey 1

☐ Perform Experiment 1 with Monkey 2

CY16 Goal – Begin simultaneous learning of artificial feedback and BMI

☐ Complete Experiment 1 and prepare manuscript

☐ Perform Experiment 2 with Monkey 1

☐ Perform Experiment 2 with Monkey 1

CY17 Goal – Obtain improved learning and performance with feedback

☐ Complete Experiment 1 and prepare manuscript

Comments/Challenges/Issues/Concerns

- Need to re-implant Monkey 1, but artifact rejection will make for a more efficient closed-loop control scheme

Budget Expenditure to Date

Projected Expenditure: $193,230
Actual Expenditure: $193,230